KOKUSHIKAN SOCIETY OF
SPORT SCIENCE
No.19, 11-19, 2019

Study

Regional differences in the incidence of severe brain damage in survivors with cardiac disease and witnessed out-of-hospital cardiac arrest

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Abstract

Background: Brain damage can occur after out-of-hospital cardiac arrest (OHCA) leading to permanent disability.

Aims: This study investigated the incidence of severe brain damage and associated risk factors in survivors with cardiac disease after OHCA.

Methods: The Utstein database for Japan was used to identify 23,640 survivors with cardiac disease and witnessed OHCA between 2005 and 2012. Survivors were assessed at 1 month. Odds ratios (ORs) for the incidence of severe brain damage according to regional variables were determined with logistic regression analysis.

Results: The incidence of severe brain damage was 37.3%. Automated external defibrillator use and cardiopulmonary resuscitation were associated with significant improvement in cerebral function; adrenaline administration and longer duration from request for transport until hospital arrival were associated with deterioration of cerebral function. Twenty of 47 prefectures showed significant ORs for the incidence of severe brain damage.

Conclusion: Regional differences in the incidence of severe brain damage were found among survivors with cardiac disease and witnessed OHCA.

Key words; Severe brain damage, survival, risk factor, out-of-hospital cardiac arrest, Utstein database, regional differences

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Abbreviations

OHCA, out-of-hospital cardiac arrest; EMS emergency medical services; CPR, cardiopulmonary resuscitation; NCF normal cerebral function; SBD severe brain damage; OR, odds ratio; CI, confidence interval

Background

Brain damage can occur after cardiac arrest due to ischemia [1, 2] and reperfusion [3], leading to permanent disability [4-8].

Out-of-hospital cardiac arrest (OHCA) cases worldwide are recorded in the Utstein database [9–11]. All OHCA patients are recorded by nationwide emergency medical services (EMS), and 7% of all deaths occur in Japan [12–16]. The Utstein database has shown that the incidence of recovery of good cerebral function after OHCA in Japan is still poor and that differences in the incidence occur at the prefectural level [17]. However, it has been difficult to explain these regional differences [18]. The extent of regional variation in OHCA outcomes suggests underlying differences in rural and urban features, patient characteristics, and patient care. Evidence from other disciplines suggests that neighborhood factors influence health outcomes [19–22]. Numerous studies have evaluated socioeconomic status and race/ethnicity and their association with OHCA survival, but the results have been inconsistent, and none has considered these factors in addition to the Utstein database variables in accounting for survival [23–24].

Aims

This study investigated regional risk factors associated with severe brain damage after OHCA in survivors with cardiac disease.

Methods

Study setting

This was a retrospective cohort study using the Utstein database in Japan.

The population of Japan is 127 million, 27.3% of whom are over 65 years of age, and the number of deaths in 2015 was 1,290,000. About 120,000 cases with OHCA were recorded by EMS, amounting to approximately 10% of all deaths. The median prefectural population is 1,668,000, with a range of 574,000-13,390,000.

The median prefectural area is 4,819 km^2, with a range of 574 km^2-78,420 km^2. Japanese are covered by a universal public health insurance system, with registration permitted by non-Japanese. The health insurance system is mainly managed by The Health Insurance (for labors) and the National Healthcare Insurance for coverage of high-cost medical expenses.

Study design

The Utstein database was used to identify survivors with cardiac disease and witnessed OHCA between 2005 and 2012 (Figure 1). We collected data on patient age, sex, initial electrocardiogram (ECG) findings, bystander cardiopulmonary resuscitation (CPR), attempted defibrillation (automated external defibrillator, AED), adrenaline administration, time of request for transport, duration from request for transport to contact with the patient (call-to-contact interval) and duration from request for transport to hospital arrival (call-to-hospital interval) ; we also assessed patient status at 1 month after OHCA. The initial finding on the ECG was divided into ventricular fibrillation or pulseless ventricular tachycardia (VF/VT) and non-VF/VT. Cases were divided into 4 types: defibrillated by a bystander (AED by public), by EMS staff (AED by EMS), by both a bystander and EMS (AED by public & EMS), or no defibrillator use. Bystander CPR cases were also divided into 4 types: conventional CPR (chest compression and artificial ventilation), chest compression only, artificial ventilation only, or none. The case study period was divided into 2005-2008 and 2009-2012 to compare elapsed times. Time of request for transport was divided into daytime (from 0900 to 1659) and nighttime (from 1700 to 0859).

Outcome definition

The outcome was cerebral function defined by the Cerebral Performance Category scale and the Glasgow-Pittsburgh Outcome Categories at 1 month after OHCA. Subjects were divided into a normal cerebral function group (NCF), with normal cerebral performance or only mild impairment (category 1 and 2), and a severe brain damage group (SBD), with severe disability or persistent vegetative state (categories 3-4) (Figure 1).

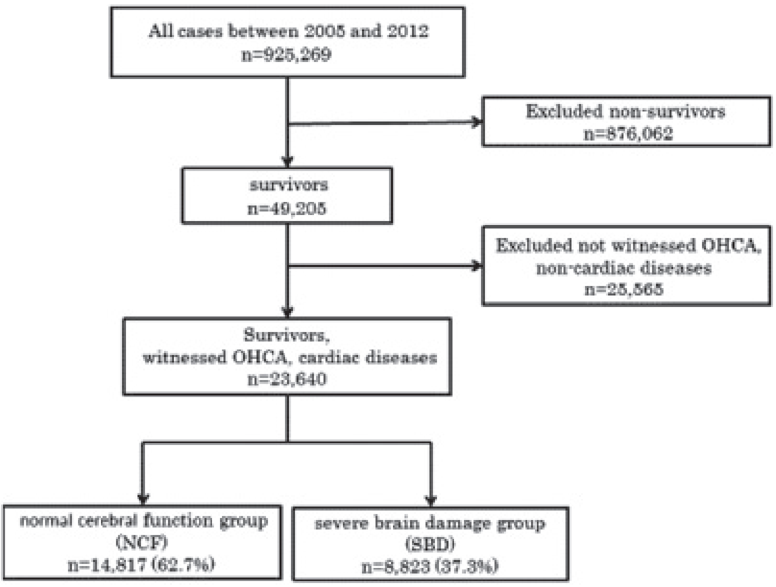

Figure 1. Flow chart

Survival rate and cerebral function

At 1 month after OHCA, cerebral and physical damage were assessed in survivors. We calculated the proportion of survivors with cerebral and physical damage among all survivors.

Risk factors for severe cerebral damage

We determined odds ratios (ORs) for NCF and SBD using multiple logistic regression analysis. The response variable was cerebral function, with 11 explanatory variables in model 1. The prefectural variables were added to model 1 in model 2. Explanatory variables implied improvement of cerebral function when the OR was >1, and deterioration when the OR was <1.

Statistical analysis

R software (ver. 3.5.0, The R foundation, Austria) was used for statistical analysis.

Ethics

The Utstein database was analyzed with the permission of the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications. This study was approved by the ethics committee of Kokushikan University (no. 27-010).

Funding

This study was partially funded by the Institute of Health, Physical Education and Sport Science, Kokushikan University.

Results

Rates of survival and severe brain damage

Of 925,269 cases, 49,205 (5.3%) were alive at 1 month after OHCA. We assessed 23,640 (2.6%) subjects with cardiac disease and witnessed OHCA. The NCF group included 14,817 (62.7%) subjects and the SBD group included 8,823 (37.3%).

Risk factors for severe brain damage

The characteristics of the groups are shown in Table 1. Multiple logistic regression analysis was used to determine ORs for cerebral function in model 1 and 2 (Table 2). Bystander AED use showed a high OR value in model 1 (Table 2, left). In model 2, 20 prefectural variables showed statistical significance when the previous variables of model 1 were similar to those of model 2 (Table 2, right).

The distribution of OR for regional factors is show in Figure 2. Twenty of 47 (42.6%) prefectures showed significantly low ORs. The same explanatory variables of model 1 and the top 10 statistically significant prefectural variables are show in Table 2. The ORs by prefecture are shown in Figure 2, with maximum and minimum values of 1.54 (95% confidence interval [CI] : 1.13-2.12) and 0.54 (0.41-

Table 1. Characteristics of SBD group and NCF group

Variable \ group	Normal cerebral function group n=14,817 n	(%)	Severe brain damage group n=8,823 n	(%)	p-value
sex male	11,147	(75.2)	5,926	(67.2)	<0.0001
female	3,670	(24.8)	2,897	(32.8)	
age 0-39 years old	1,393	(9.4)	496	(5.6)	<0.0001
age 40-64	6,267	(55.8)	2,516	(28.5)	
age 65-74	3,492	(23.6)	2,185	(24.8)	
age 75-84	2,569	(17.3)	2,380	(27.0)	
age 85-	1,095	(12.4)	1,245	(14.1)	
night time at occurrence	7,268	(49.1)	4,496	(51.0)	0.0046
non-VTVF at the first findings	8,434	(56.9)	3,838	(43.5)	<0.0001
CPR conventional	2,510	(16.9)	1,217	(13.8)	<0.0001
CPR chest compression	4,389	(29.6)	2,172	(24.6)	
CPR respiration	97	(1.7)	11	(0.9)	
AED by citizen	980	(6.6)	126	(1.4)	<0.0001
AED by citizen and EMS	467	(5.3)	112	(1.3)	
AED by EMS	9,098	(27.8)	4,125	(46.8)	
call contact interval>10min	12,760	(86.1)	8,547	(96.9)	<0.0001
call hospital interval>60min	13,980	(94.4)	8,492	(96.2)	<0.0001
Adrenaline administration	758	(5.1)	1,326	(15.0)	<0.0001
2009-2012/ 2005-2008	9,120	(61.6)	4,875	(55.3)	<0.0001

0.72); all OR values and 95% CIs are shown in Figure 2.

Discussion

Factors associated with improvement and deterioration of cerebral function

In this study, factors associated with improvement of cerebral function after OHCA were AED use and CPR method. Bystander AED use showed an OR of 5.21 and 95% CI of 4.29-6.38; these were the highest values among methods of CPR. AED use by both a bystander and EMS crew showed an OR of 3.48 and 95% CI of 2.77-4.40. Corresponding values for AED use by an EMS crew were 2.08 and 1.89-2.30. This suggests that earlier AED use results in better cerebral function after OHCA. The respective OR and 95% CI values for chest compression CPR and conventional CPR were 1.16 (1.08-1.24) and 1.11 (1.02-1.21) these were moderately statistically significant. Respective OR and 95% CI values for 2009-2012 compared to 2005-2008 were 1.42 (1.34-1.51). This variable was used by considering an increase in elapsed time to account for complications. Several reports showed similar

Table 2. Risk factors of severe brain damage through multiple logistic regression

variable	model 1				model 2			
	OR	lower 95%CI	upper 95% CI	p-value	OR	lower 95%CI	upper 95% CI	p-value
sex female / male	0.90	0.85	0.96	0.0019	0.90	0.84	0.96	0.0013
age 40- 64 years	0.88	0.79	0.99	0.0404	0.88	0.78	0.99	0.0409
age 65-74 years	0.63	0.56	0.71	<0.0001	0.63	0.56	0.71	<0.0001
age 75-84 year old	0.49	0.43	0.55	<0.0001	0.49	0.43	0.55	<0.0001
age >=85 years	0.45	0.39	0.52	<0.0001	0.45	0.39	0.52	<0.0001
nighttime / daytime	0.97	0.91	1.02	0.2565	0.97	0.92	1.03	0.2940
non-VTVF/ VTVF	0.93	0.84	1.02	0.1327	0.94	0.85	1.03	0.1898
CPR conventional	1.11	1.02	1.21	0.0215	1.09	1.00	1.19	0.0440
CPR compression	1.16	1.08	1.24	0.0000	1.15	1.07	1.23	0.0001
CPR respiration	0.77	0.56	1.06	0.1059	0.76	0.55	1.05	0.0902
AED by citizen	5.21	4.29	6.38	<0.0001	5.13	4.22	6.30	<0.0001
AED by EMS	2.08	1.89	2.30	<0.0001	2.07	1.88	2.29	<0.0001
AED by citizen & EMS	3.48	2.77	4.40	<0.0001	3.49	2.78	4.42	<0.0001
call to contact/<10min	1.06	0.97	1.15	0.1845	1.06	0.98	1.16	0.1391
call to hospitals /<60min	0.66	0.58	0.76	<0.0001	0.67	0.58	0.77	<0.0001
Adrenaline administration	0.26	0.23	0.29	<0.0001	0.25	0.23	0.28	<0.0001
2009-2012/2005-2008	1.42	1.34	1.51	<0.0001	1.42	1.34	1.51	<0.0001
prefecture a					0.55	0.42	0.72	<0.0001
prefecture b					0.63	0.51	0.78	<0.0001
prefecture c					0.68	0.57	0.82	<0.0001
prefecture d					0.58	0.45	0.75	<0.0001
prefecture e					1.38	1.18	1.61	<0.0001
prefecture f					0.72	0.62	0.84	<0.0001
prefecture g					0.56	0.42	0.75	0.0001
prefecture h					0.62	0.49	0.80	0.0001
prefecture i					0.76	0.66	0.89	0.0004
prefecture j					0.56	0.40	0.77	0.0004

The Top ten ORs of prefectures are shown in model 2, which were ordered ascendingly by p-value.

results among all OHCA cases in Japan [13, 15, 16].

In contrast, factors associated with deterioration after OHCA were female sex (0.90, 0.85-0.96), older age, duration from request for transport until hospital arrival, and adrenaline administration. The ORs by age group decreased proportionally with increasing age. Adrenaline has a strong inotropic and chronotropic action; however, the OR for adrenaline administration was low 0.26 (0.23-

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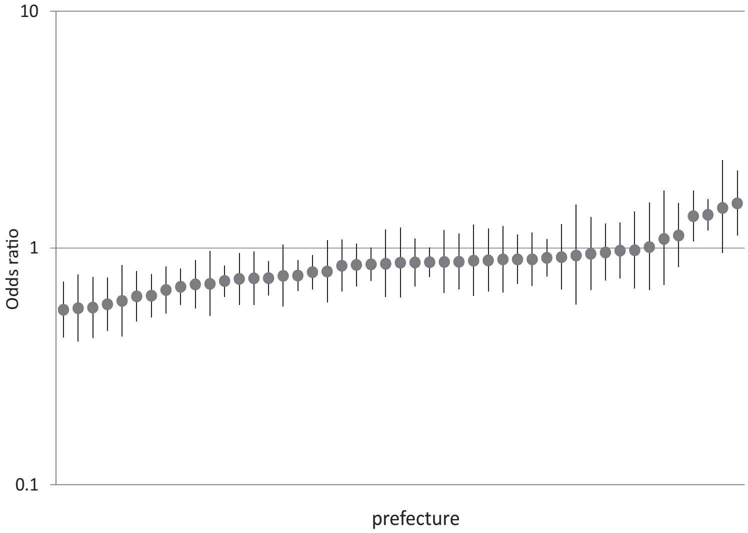

ORs (circle)and 95%CIs (line) of each prefecture ordered by p-value were demonstrated in the figure 2. 20 prefectures were statistically significant. Four prefectures showed improving factors and 16 prefectures showed deteriorating factors.

Figure 2. Odd ratio and 95%CI of each prefecture ordered ascendingly in model 2

0.29). This suggests that adrenaline was selectively used in critically ill patients who did not respond to AED use.

Regional factors

We surveyed 47 prefectures to identify regional factors. Four prefectures were associated with significant improvement and 16 were associated with significant deterioration in cerebral function after OHCA. Therefore, regional differences and factors should be considered in assessment of cerebral function after OHCA [17]. Okubo reported regional differences by prefecture after OHCA, but was unable to demonstrate that these differences were associated with CPR training of the public [18]. Conventional statistical analysis may help in identifying regional factors among many variables in a large-scale database. Regional differences should be considered in further studies when risk factors associated with OHCA are surveyed.

Limitations

This study had limitations. First, this was an observational cohort study, and not a randomized control trial.

Second, the Utstein template does not include the diagnosis as a variable, even when variables of cardiac or non-cardiac disease are present. Therefore, we could not select cases by diagnoses.

Third, many reports have demonstrated that socioeconomic status (SES) influences healthcare outcomes [24-29]. We did not survey variables of SES such as education level, income, and savings as these variables are not included in the Utstein database, and we could not compare the Utstein data with individual claims data.

Fourth, this study assessed survivors with cardiac disease after witnessed OHCA. As the survival rate was only 2.8%, a 0-inflated Poisson model or generic mixture model should be considered in the analysis [30].

Conclusion

The incidence of severe brain damage among survivors with cardiac disease and witnessed OHCA was 37.8% in Japan. Regional differences in severe brain damage are found at the prefectural level.

Conflict of interests

There were no conflict of interests through the development of this stady.

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